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CHAPTER 6

PHYSIOLOGICAL MOVEMENT DISORDER-LIKE FEATURES DURING TYPICAL MOTOR DEVELOPMENT

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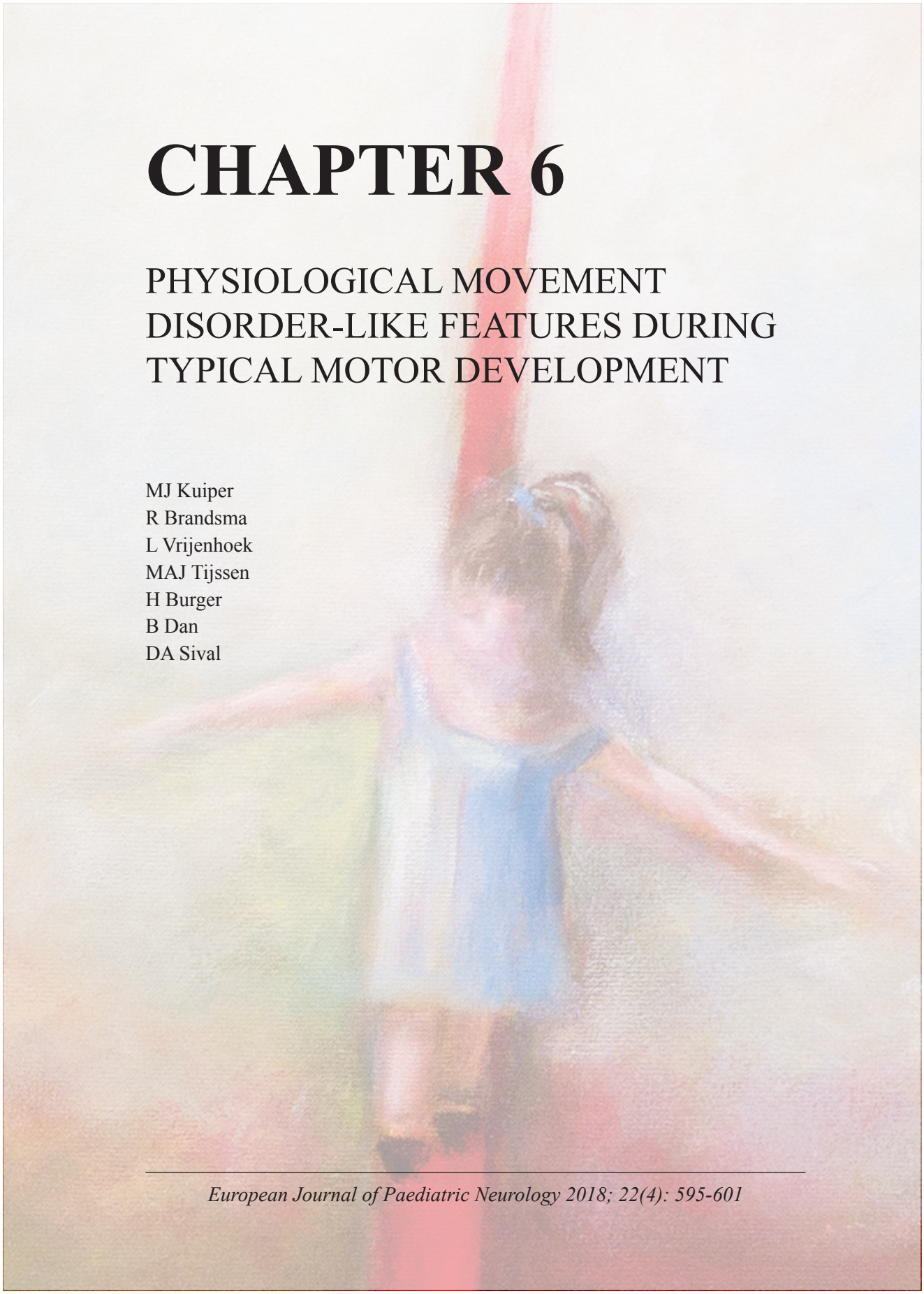

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ABSTRACT

AIM: To compare physiological age-relatedness between dyskinesia (dystonia/choreoathetosis), dystonia and ataxia rating scale scores in healthy children.

METHODS: Three movement disorders specialists quantified dyskinetic-like features in healthy children (n=52; 4-16 years) using the Dyskinesia Impairment Scale (DIS= DIS-choreoathetosis (DIS-C) + DIS-dystonia (DIS-D)). We compared the age-related regression coefficients of the DIS with data processed from previous studies on dystonia and ataxia rating scales (Burke-Fahn-Marsden Movement and Disability Scales (BFMMS and BFMDS) and Scale for Assessment and Rating of Ataxia (SARA), International Cooperative Ataxia Rating Scale (ICARS) and Brief Ataxia Rating Scale (BARS)).

RESULTS: Dyskinetic scores were obtained in 79% (DIS); 65% (DIS-D) and 17% (DIS-C) versus dystonic and ataxic scores in 98% (BFMMS) and 89% (SARA/ICARS/BARS) of the children. Age-related DIS and DIS-D scores (B=-0.90 and 0.77; $p<0.001$) were correlated with age-related BFMMS scores (B=-0.49; $p<0.001$; $r=0.87$; $p<0.001$), whereas DIS-C scores were age-independent. Ataxic scores revealed stronger age-related regression coefficients than dyskinetic and dystonic scores (4-8 years; $p<0.05$).

CONCLUSIONS: In healthy children, comparison between physiological dyskinesia, dystonia and ataxia rating scale scores revealed: 1. inverse age-relatedness for dystonic and ataxic scores, but not for choreoathetotic scores, 2. interrelated dystonic DIS-D and BFMMS scores, 3. the strongest age-related expression by ataxic scores. In healthy children, these physiological movement disorder-like features are interpreted as an expression of the developing underlying motor centres.

INTRODUCTION

Throughout childhood, physiological characteristics of motor patterns may reveal a resemblance to movement disorder features, including infantile fidgety movements (choreoathetosis), toddlers gait (ataxia) and the asymmetrical tonic neck reflex (dystonia).[1-9] These features are functionally attributed to the developing central nervous system (CNS), including the formation and shaping of motor networks between the basal ganglia, cerebral cortex and cerebellum.[4-6] Such physiological movement disorder-like features may often meet the scoring criteria of movement disorder rating scales. This suggests that rating scale scores in children are not only influenced by the movement disorder, but also by the age of the child. Longitudinal paediatric rating scale scores could thus run the risk of over-interpretation, especially when small longitudinal "improvements" are interpreted as "therapeutic".[10] For adequate interpretation of paediatric rating scales, we have recently determined the age-dependent effect on ataxia (SARA, ICARS, BARS) and dystonia (BFMMS and BFMDS) rating scales in healthy, typically developing children (4-16 years of age).[4,5] Outcomes revealed an inverse relationship between the rating scale scores and age, with a disappearance of ataxic- and dystonic-like features before adulthood.[4-6] Under the premise that the age-related physiological movement disorder-like features are attributable to the developing motor system, we hypothesized that other features of paediatric movement disorders, such as dyskinetic-like (i.e. choreoathetotic- and dystonic-like) features, could also be systematically present. In healthy, typically developing children (4-16 years of life), we therefore quantified dyskinetic-like features, by application of the newly developed Dyskinesia Impairment Scale (DIS); consisting of the summed choreoathetosis (DIS-C) and dystonia (DIS-D) subscales.[11]recruited from special schools for children with motor disorders, were included. Exclusion criteria were changes in muscle relaxant medication within the previous 3 months, orthopaedic or neurosurgical interventions within the previous year, and spinal fusion. Interrater reliability was verified by two independent raters. For interrater reliability, intraclass correlation coefficients were assessed. Standard error of measurement, the minimal detectable difference, and Cronbach\u2019s alpha for internal consistency were determined. For concurrent validity of the DIS dystonia subscale, the Barry\u2013Albright Dystonia Scale was administered. RESULTS: The intraclass correlation coefficient for the total DIS score and the two subscales ranged between 0.91 and 0.98 for interrater reliability. The reliability of the choreoathetosis subscale was found to be higher than that of the dystonia subscale. The standard error of the measurement and minimal detectable difference values were adequate. Cronbach\u2019s alpha values ranged from 0.89 to 0.93. Pearson\

u2019s correlation between the dystonia subscale and Barry\u2013Albright Dystonia Scale was 0.84 ($p<0.001$ Assuming that DIS-D (dystonia scores) would relate with paediatric age, we hypothesized that DIS-D and BFMMS scores would reflect the same age-related pattern and would be interrelated. Furthermore, following the unique developmental trajectories of the underlying motor centres (basal ganglia, cerebellum and cortex), we reasoned that age-related patterns would differ between dystonic, ataxic and choreoathetotic scores.

Altogether, in healthy, typically developing children (4-16 years of age), we aimed (1) to investigate the age-related influence on dyskinesia (DIS, DIS-D and DIS-C) rating scale scores and, (2) to compare the age-related effect between dyskinesia (DIS, DIS-D and DIS-C), dystonia (BFMMS and BFMDS) and ataxia (SARA, ICARS and BARS) rating scale scores. We reasoned that comparative insight in the age-related effect on rating scale scores would contribute to the understanding of the functional expression of the developing motor centres and would also contribute to reliable interpretation of longitudinal rating scale scores in children.

METHODS

PARTICIPANTS

After written informed consent by the parents and children (when older than 12 years of age), we included 52 healthy, typically developing children between 4 and 16 years of age, consisting of 2 males and 2 females (n=4) per year of age. In the absence of existing quantitative age-related DIS data in healthy children, we based our sample size on previously published data on inter-observer agreement in patients with dyskinetic cerebral palsy.[11] Detecting an Intraclass Correlation Coefficient (ICC) of 0.90 for the DIS or over the null hypothesis of a moderate ICC of 0.60 (0.96 published for DIS in young patients with dyskinetic cerebral palsy[11]), a sample size of 31 children would be needed. Analogous to previous studies determining age-related influences on ataxia and dystonia rating scale scores, we included 52 healthy children using the same inclusion and exclusion criteria.[4,5] Inclusion criteria were: healthy children, attending mainstream education at a regular school. Before deciding on study inclusion, the parents of included children completed a small questionnaire concerning neurological, skeletal and/or muscle disorder diagnosis, prescribed medication, sporting activities, school performances and parental education level. Participants were excluded from the study if they: (1) were diagnosed with a neurological or skeletal disorder; (2) showed a positive Gower's sign; (3) received medication with known side-effects

on motor behaviour; (4) presented with developmental delay or cognitive impairment imposing the need for extra support by special schools. Analogous to previous age validation studies of ataxia and dystonia rating scales,[4,5] we did not exclude paediatric behavioural diagnoses such as Attention Deficit Hyperactive Disorder (ADHD) or Attention Deficit Disorder (ADD). We recruited participants through open advertisements at regional schools. Participants characteristics were compared with participant characteristics from previous studies determining age-related influences on ataxia and dystonia rating sale scores. [4,5]

PROCEDURE

The study was approved by the medical ethical committee of the University Medical Center Groningen, the Netherlands. Collected physiognomic data included length, weight, and head circumference.

DIS SCORES IN HEALTHY CHILDREN

In accordance with the standardized DIS video protocol,[11] we video-recorded motor tasks in 52 healthy children, in a quiet place. The Dyskinesia Impairment Scale (DIS) is a recently developed rating scale, consisting of the summed score of the dystonia (DIS-D) and choreoathetosis (DIS-C) subscales.[11] These subscales quantify the duration and amplitude of dystonia and choreoathetosis, respectively, in 12 body regions, involving the eyes, mouth, neck, trunk, proximal and distal limbs on each side.[11]

After DIS assessment training, three independent movement disorder specialists scored the video recordings offline, according to exact DIS guidelines.[11] We determined inter-observer agreement and subsequently associated median DIS outcomes (per subscale) with age and socio-economic factors.

AGE-RELATED COMPARISON BETWEEN DYSKINESIA, DYSTONIA AND ATAXIA RATING SCALES

In the study group, we calculated the percentage of children with dyskinetic, dystonic and ataxic-like features (dystonic and ataxic percentages were processed from historic data, obtained in an identical way).[4,5] For descriptions of movement disorder-like features and for rating scale information, see Appendix A and B, respectively. Subsequently, we compared the age-related influence between dyskinetic- (DIS, DIS-D and DIS-C), dystonic- (BFMMS and BFMDS) and ataxic-like features (SARA, ICARS and BARS) by regression coefficients. As children had previously revealed the strongest age-related effects between the age of 4 to 8

years,[4,5] we stratified age-related outcomes between the youngest (4–8 years) and oldest (9-16 years) paediatric subgroups.

STATISTICAL ANALYSIS

We performed statistical analyses using PASW Statistics 22 for Windows (SPSS Inc., Chicago IL). We compared the participant characteristics of the present study with previously published studies with the Chi-Square test. To test the reliability of the DIS scores, we determined inter-observer agreement of scores by ICC, using the two-way mixed model and single measurement coefficients. We assessed normality of the distribution of the DIS, DIS-D and DIS-C outcomes, both graphically and using the Kolmogorov-Smirnov test. We tested DIS outcomes for homoscedasticity (i.e. the homogeneity of the residuals after performing regression analysis)[12] using the Koenker test. Subsequently, we performed multivariate regression analysis on the influence of age, gender, school performances, sporting activities and parental education level on DIS outcomes. We determined the age at which DIS outcomes reached the optimum score by performing a polynomial trend analysis with a one phase decay or logarithmic analysis (depending on the best fitted trend line) [Graphpad Prism 5, Version 5.04]. We correlated DIS-D with BFMMS with Pearson's or Spearman's rank correlation coefficient (when outcomes were not normally distributed). For the comparison between age-related factors of the rating scales, we standardized the scales by transforming the scores for each rating scale into z-scores and performed linear regression of the z-scores on age. Subsequently, we compared the regression coefficients of the different rating scales and tested its statistical significance using the t-test (in each age (sub)group). P-values of <0.05 (two-sided) were considered to indicate statistical significance.

RESULTS

CHARACTERISTICS OF INCLUDED CHILDREN

For characteristics of the included children, see supplementary Table I. Socioeconomic factors (school performances and sports participation) did not significantly influence DIS scores. Participants' characteristics did not significantly differ between the presently included children for the DIS assessment and previously included children for the BFMMS, BFMDS, SARA, ICARS and BARS assessments ($p>0.05$).[4,5] ADHD and/or school performances below average did not influence the DIS-D and DIS-C scores, analogous to identically reported paediatric

data on paediatric dystonia (BFMMS and BFMDS) and ataxia (SARA, ICARS and BARS) rating scale scores, see supplementary Table II.

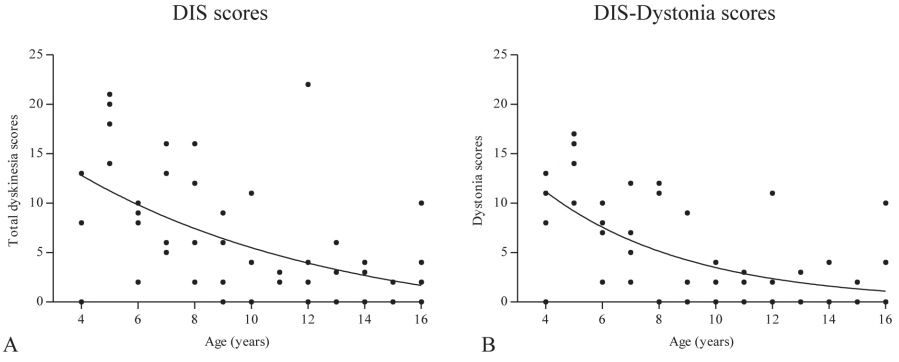
INTER-OBSERVER AGREEMENT OF DIS SCORES

Inter-observer agreement revealed statistically significant results: ICCs ($p < 0.01$) of 0.42 (DIS), 0.46 (DIS-D) and 0.23 (DIS-C).

AGE-DEPENDENCY OF DIS SCORES

DIS, DIS-D and DIS-C scores were not normally distributed ($p < 0.001$) and revealed no deviation of homoscedasticity ($p > 0.05$). DIS (range: 0 - 22; mean: 6.2) and DIS-D scores (range: 0 - 17; mean: 4.5) were significantly predicted by age (B = -0.90, $p < 0.001$ and B = -0.77, $p < 0.001$, respectively). Age explained 30.4% (DIS) and 33.9% (DIS-D) of differences in scores. The associations between age and median DIS and DIS-D scores showed a consistent age-related effect until 16 years of age for both (sub)scales, see figure 1A and 1B. DIS-C scores (range: 0 – 10; mean: 1.1) were not significantly predicted by age (B = -0.11, $p = 0.162$).

Figure 1. Dyskinesia Impairment Scale (DIS) scores related to age



DIS (A) and DIS-Dystonia (B) scores related to age. Data points represent median scores per child. DIS and DIS-Dystonia scores are age-dependent until 16 years of age (p<0.001).

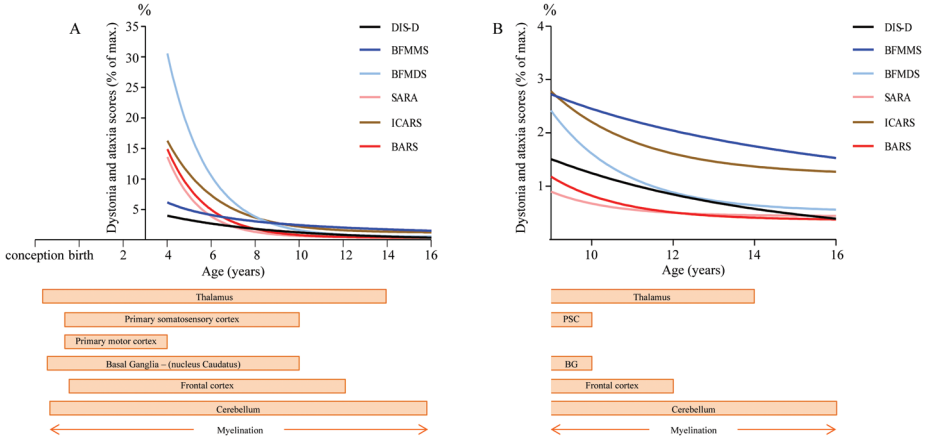
AGE-RELATED COMPARISON BETWEEN DYSKINESIA (DIS), DYSTONIA (BFMMS AND BFMDS) AND ATAXIA RATING SCALE (SARA, ICARS AND BARS) SCORES

In children between 4–16 years of age, 79%, 65% and 17% of the children revealed DIS scores above the optimum score 0 (DIS, DIS-D and DIS-C, respectively) versus 98% and 89% of the children with dystonic (BFMMS) and ataxic (SARA, ICARS and BARS) scores above the optimum score 0 (processed from previous

study data[4,5]), respectively. For definitions of movement disorder-like features and scored video examples, see Appendix A and video recordings. Dystonia rating scale scores DIS-D and BFMMS were significantly correlated: $r = 0.87$ ($p < 0.001$).

Stratification of the standardized regression coefficients per age subgroup revealed significantly higher ataxic than dystonic scores in the youngest children (4-8 years; $p<0.05$), see Table I, supplementary Table III and figure 2. In the oldest age subgroup (9-16 years) and the total group (4-16 years), the standardized regression coefficients of DIS, DIS-D, BFMMS, SARA, ICARS and BARS revealed no statistically significant differences ($p > 0.05$), see Table I and supplementary Table IV and V.

Figure 2. Movement disorder rating scale age-relatedness in perspective of the physiologic brain maturation



Movement disorder rating scale scores are provided as the % of the maximum score per rating scale. The age-relatedness of movement disorder rating scales in children between 4 – 16 years (A) and between 9 – 16 years of age (B) in perspective of motor centre maturation (determined by a peak in gray matter volume on MRI27). Dystonia- and ataxia- motor rating scales reach the "adult" optimum value around 12 and ≥16 years of age, respectively. DIS-D = Dyskinesia Impairment Scale-Dystonia subscale; BFMMS = Burke-Fahn-Marsden Movement Scale; BFMDS = Burke-Fahn-Marsden Disability Scale; SARA = Scale for the Assessment and Rating of Ataxia; ICARS = International Cooperative Ataxia Rating Scale; BARS = Brief Ataxia Rating Scale; BG = Basal Ganglia; PSC = Primary Somatosensory Cortex

The dystonia (DIS-D, BFMMS) and ataxia (SARA, ICARS, BARS) rating scale scores approached the "adult" optimum value of zero at about 16 and 12 years of age, respectively. Between 12 and 16 years of age, the dystonia and ataxia rating scales scores revealed a decrease of 0.5% of the maximum score ($p > 0.05$), see figure 2.

Table I. Regression coefficients for z-scores of dyskinesia, dystonia and ataxia rating scale scores predicted by age

	B (SE) 4 – 16 years	B (SE) 4 – 8 years	B (SE) 9 – 16 years
DIS			
Total scores	-0.15 (0.03)**	-0.12 (0.16)	-0.05 (0.06)
Dystonia subscores	-0.14 (0.05)*	-0.25 (0.16)	-0.03 (0.05)
Choreoathetosis subscores	-0.05 (0.05)	0.16 (0.16)	-0.11 (0.08)
BFMDRS			
Movement scale (BFMMS)	-0.19 (0.03)**	0.06 (0.13)	-0.05 (0.03)
Disability scale (BFMDS)	-0.18 (0.03)**	-0.67 (0.12)**	-0.02 (0.03)
Ataxia rating scales			
SARA	-0.18 (0.03)**	-0.64 (0.14)**	-0.04 (0.01)*
ICARS	-0.20 (0.02)**	-0.66 (0.10)**	-0.08 (0.02)*
BARS	-0.19 (0.03)**	-0.74 (0.10)**	-0.03 (0.02)

*Linear regression results for z-scores of movement disorder rating scales scores predicted by age; DIS = Dyskinesia Impairment Scale; BFMDRS = Burke-Fahn-Marsden Dystonia Rating Scale; SARA = Scale for the Assessment and Rating of Ataxia; ICARS = International Cooperative Ataxia Rating Scale; BARS = Brief Ataxia Rating Scale; B = regression coefficient; SE = standard error; * p<0.01; ** p<0.001*

DISCUSSION

In healthy, typically developing children of 4 to 16 years of age, we compared the influence of age on physiological movement features resembling dyskinesia (i.e. dystonia and choreoathetosis), dystonia and ataxia. Dystonic DIS-D and BFMMS scores were strongly correlated ($r = 0.87$), analogous to previously reported correlations between SARA, ICARS and BARS (range: $r = 0.68 – 0.82$) scores.[4] Both dystonic (DIS-D, BFMMS, BFMDS) and ataxic (SARA, ICARS, BARS) scores appeared inversely related with age, with the strongest age-related effects on ataxia rating scale scores in the younger children (4-8 years of age). In contrast to age-dependent dystonic- and ataxic-like features, more sparsely occurring choreoathetotic (DIS-C) scores appeared age-independent.

Comparing inter-observer agreement (ICC) on DIS scores between healthy children (DIS: 0.42, DIS-D: 0.46, DIS-C: 0.23) and children with dyskinetic cerebral

palsy (DIS: 0.96, DIS-D: 0.91, DIS-C: 0.98)[11], revealed lower ICC values in the first group, although still significant. This can be attributed to the smaller scoring range in healthy children compared to children with a movement disorder, causing a mathematic reduction in the ICC outcome.[12] This explanation is supported by the high percentage of agreement when outcomes would be subdivided into subgroups of 5% of the maximum score (DIS: 96.1%; DIS-D: 88.5% and DIS-C: 97.4%). Thus, although absolute ICC values may seem relatively small, the percentage of inter-observer agreement appears relatively high.

In healthy children (4-16 years of age), physiological dystonic DIS-D scores revealed an age-dependent effect, analogous with previously reported age-relatedness of BFMMS scores and functional BFMDS scores.[5] These physiologically age-related scores are attributed to CNS development, including the basal ganglia and cerebellum.[5] Throughout childhood, the basal ganglia are developing and strengthening by synaptic elimination and myelination of connections.[13-15] These maturational processes are likely to be expressed by a reduction in co-contractions and dystonic-like features.[2,3,5,7] In contrast to age-dependent dystonic-like features, paediatric choreoathetotic scores (DIS-C) were sparsely present (mean: 1.1 point; range: 0-10 points (3.5% of maximum score)) and lacked an age-dependent effect. This may seemingly contrast with the commonly reported choreoathetotic-like fidgety movements in typically developing neonates, which are considered as an integral part of healthy infantile motor development.[2,16,17] The underlying mechanism for the early disappearance of these physiological choreoathetotic-like movement patterns remains elusive. It has been suggested that increased inhibition by the cerebral cortex and basal ganglia are involved.[15,18] Hypothetically, this may concur with a gradual shift from subplate activity (which induces general movement complexity and variation) to activity of developing neural networks centred in the cortical plate.[19]

Comparing age-dependency between choreoathetotic-, dystonic- and ataxic-like features, revealed a stronger age-related influence on ataxic- than on dystonic-like features in the youngest age-subgroup (4-8 years), whereas choreoathetotic-like features lacked age-dependency. These age-related differences in physiologically occurring movement disorder-like features are attributed to specific developmental patterns of the underlying motor centres. During brain development, the grey matter volume of the putamen and globus pallidus reaches a peak before 8 years of age,[20] the caudate nucleus between 8 and 10 years of age,[14,21] and the grey matter volume of the cerebellum by 15-18 years of age.[21] In perspective of the relatively late maturation of the cerebellum compared to the basal ganglia, one could easily

understand the relatively stronger age-related effect on ataxic scores in young children. Thus, following the unique age-related profiles of dystonic, ataxic and choreoathetotic rating scale scores, one could approximately derive the underlying developmental patterns of the associated motor centres and networks (basal ganglia, cerebellum and cerebral cortex).

In healthy children (4-16 years of age), physiological age-related movement disorder-like features are thus interpretable from developmental perspective of the corresponding motor centres. Previously, it has been indicated that children with ADHD or learning disabilities may reveal "soft neurological signs".[22] As we deliberately did not exclude for ADHD and/or learning disabilities as part of a regular study sample of school aged children, it could be argued that this might have influenced the outcomes. However, in the presently included study group (and also in the previous study groups for the dystonia and ataxia rating scales studies),[4,5] the prevalence of ADHD (present study: 0%; previous studies: 1%) and learning disabilities (present study: 4%; previous studies: 4%) was lower than in the average Dutch population (ADHD: 3-5% and learning disabilities: 25%). Furthermore, the included children with ADHD and/or learning disabilities scored within a small range (± 1 SD) from the mean, and exclusion of these children resulted in the same age-related scores and regression coefficients. From this data it may be derived that the age-relatedness of the presently investigated movement disorder rating scale scores do not represent "soft neurological signs", a concept that may imply a disorder, but rather the influence by "physiological immaturity" during typical neurodevelopment in healthy children.

We recognize several limitations to the present study. First, the number of included children is relatively small. However, we have recently replicated the SARA pilot study,[4] that was based on exactly the same methods in a large international setting (n=156), with only 1% difference in explained SARA-score variance by age.[6] Second, in studies with (presumably) healthy control children, one could never provide a 100% proof that the included children are really healthy. However, one may state that, before entering the study, all children fulfilled the predefined inclusion criteria and were considered to be healthy by their parents and teachers. Although the presently included children were screened for ADHD and learning difficulties by an interrogation list, and although all included children attended a regular Dutch school system with easy access to behavioural and/or cognitive assessment, one could still argue that some of the children might have "missed" the diagnosis ADHD and/or learning disabilities at study inclusion. However, as the study group also revealed a much smaller percentage of "below average" school

achievements than the average Dutch school children (4% versus 25%, respectively) this appears less likely. Third, we are aware that we deliberately applied movement disorder rating scales as an instrument to measure physiological motor development in healthy children. Although this is not the original intention of the scales, the assessors scored the observed movement features strictly according to the official rating scale guidelines. As all ICC values were significant, we suggest that the presented age-related outcomes could be interpreted as indicative.

In conclusion, the present study demonstrates a consistent age-related effect on dystonia (DIS-D, BFMMS, BFMDS) and ataxia (SARA, ICARS, BARS) rating scale scores, whereas sparsely occurring choreoathetosis (DIS-C) rating scale scores are age-independent. Age-related comparison between dystonia and ataxia rating scale scores reveals a stronger age-dependent effect on ataxia scores in children of 4 to 8 years of age. We conclude that physiological paediatric movement disorder-like features are transiently present, as a functional expression of the underlying development of the corresponding motor centres.

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Supplementary Table I. Patient characteristics

	DIS subjects (n = 52)	Historic data* (n = 156)	Dutch pop. (%)
Age (years)			
Range	4-16	4-16	
Mean (SD)	10 (4)	10 (4)	
ADHD diagnosis, *n (%)*	0 (0%)	2 (1.3%)	3-5%
Sporting activities, *n (%)*			
< 1 hour	7 (13.5%)	15 (9.6%)	45.0%
1-2 hours	20 (38.5%)	51 (32.7%)	23.2%
2-4 hours	15 (28.8%)	40 (25.6%)	14.7%
4-6 hours	7 (13.5%)	29 (18.6%)	7.8%
> 6 hours	3 (5.8%)	19 (12.2%)	9.3%
Missing values	0 (0%)	2 (1.3%)	
School performances, *n (%)*			
Above average (A/B)	27 (51.9%)	92 (59.0%)	46.6%
Average (C)	20 (38.5%)	49 (31.4%)	28.1%
Below average (D/E)	2 (3.8%)	9 (5.8%)	25.3%
Missing values	3 (5.8%)	6 (3.8%)	

*Sporting activities are indicated in hours per week; school performances are indicated as mean achievements; SD = standard deviation; *Historic data = data of subjects included in the BFMMS, BFMDS, SARA, ICARS and BARS studies; pop. = population. Dutch population numbers were determined from Trimbos Institute, Central Statistical Office of the Netherlands and National Kompas. DIS = Dyskinesia Impairment Scale; BFMMS = Burke-Fahn-Marsden Movement Scale; BFMDS = Burke-Fahn-Marsden Disability Scale; SARA = Scale for the Assessment and Rating of Ataxia; ICARS = International Cooperative Ataxia Rating Scale; BARS = Brief Ataxia Rating Scale*

Supplementary Table II. Descriptive statistics and regression coefficients of rating scale scores with and without participants with ADHD and/or learning disabilities

	Total group	Total group – ADHD	Total group – learning disabilities	Total group – ADHD and learning disabilities
DIS-Total				
Range	0 – 4	=	0 – 4	=
Mean	1.1		1.1	
B (SE)	-0.15 (0.03)		-0.14 (0.03)	
DIS-D				
Range	0 – 6	=	0 – 6	=
Mean	1.6		1.5	
B (SE)	-0.15 (0.03)		-0.15 (0.03)	
DIS-C				
Range	0 – 3	=	0 – 3	=
Mean	0.4		0.4	
B (SE)	-0.05 (0.162)		-0.06 (0.04)	
BFMMS				
Range	1 – 11	=	1 – 11	=
Mean	4.6		4.5	
B (SE)	-0.19 (0.03)		-0.19 (0.03)	
BFMDS				
Range	0 – 40	0 – 40	0 – 33	0 – 33
Mean	6.0	6.1	5.4	5.5
B (SE)	-0.18 (0.03)	-0.18 (0.03)	-0.17 (0.02)	-0.17 (0.03)
SARA				
Range	0 – 20	0 – 20	0 – 20	0 – 20
Mean	2.5	2.6	2.7	2.8
B (SE)	-0.18 (0.03)	-0.18 (0.03)	-0.21 (0.03)	-0.21 (0.03)
ICARS				
Range	0 – 19	0 – 19	0 – 19	0 – 19
Mean	4.4	4.4	4.6	4.7
B (SE)	-0.20 (0.02)	-0.20 (0.02)	-0.23 (0.03)	-0.23 (0.03)
BARS				
Range	0 – 17	0 – 17	0 – 17	0 – 17
Mean	2.9	3.0	3.1	3.2
B (SE)	-0.19 (0.03)	-0.19 (0.03)	-0.21 (0.03)	-0.21 (0.03)

Range, mean and regression coefficients for percentage of maximum scores and z-scores of all rating scales, respectively. Exclusion of participants with ADHD and/or learning disabilities reveals similar outcomes as inclusion of these participants for all rating scales. Learning disabilities = below average school performances; DIS = Dyskinesia Impairment Scale; DIS-D = Dystonia subscale of DIS; DIS-C = choreoathetosis subscale of DIS; BFMMS = Burke-Fahn-Marsden Movement Scale; BFMDS = Burke-Fahn-Marsden Disability Scale; SARA = Scale for the Assessment and Rating of Ataxia; ICARS = International Cooperative Ataxia Rating Scale; BARS = Brief Ataxia Rating Scale; B = regression coefficient; SE

Supplementary Table III. P-values for comparing regression coefficients between dyskinesia, dystonia and ataxia motor rating scales in children between 4 - 8 years of age

	DIS	DIS-D	BFMMS	SARA	ICARS	BARS
DIS		0.57	0.38	0.02*	0.005*	0.002*
DIS-D			0.14	0.07	0.04*	0.01*
BFMMS				<0.001*	<0.001*	<0.001*
SARA					0.93	0.57
ICARS						0.56
BARS						

*Regression coefficients revealed significantly higher outcomes for the ataxia rating scales (SARA, ICARS and BARS) than for the dyskinesia (DIS) and dystonia rating scales (DIS-D and BFMMS) in children between 4 - 8 years of age (except SARA ≈ DIS-D); * statistically significant differences between regression coefficients ($p < 0.05$); DIS = Dyskinesia Impairment Scale; DIS-D = DIS Dystonia subscale; BFMMS = Burke-Fahn-Marsden Movement Scale; SARA = Scale for the Assessment and Rating of Ataxia; ICARS = International Cooperative Ataxia Rating Scale; BARS = Brief Ataxia Rating Scale*

Supplementary Table IV. P-values for comparing regression coefficients between dyskinesia, dystonia and ataxia motor rating scales in children between 9 - 16 years of age

	DIS	DIS-D	BFMMS	SARA	ICARS	BARS
DIS		0.72	0.96	0.89	0.60	0.67
DIS-D			0.61	0.71	0.27	1
BFMMS				0.76	0.48	0.47
SARA					0.16	0.49
ICARS						0.08
BARS						

Regression coefficients of dyskinesia (DIS), dystonia (DIS-D and BFMMS) and ataxia (ICARS, SARA and BARS) rating scales revealed no significant differences in children between 9 - 16 years of age; DIS = Dyskinesia Impairment Scale; DIS-D = DIS Dystonia subscale; BFMMS = Burke-Fahn-Marsden Movement Scale; SARA = Scale for the Assessment and Rating of Ataxia; ICARS = International Cooperative Ataxia Rating Scale; BARS = Brief Ataxia Rating Scale

Supplementary Table V. P-values for comparing regression coefficients between dyskinesia, dystonia and ataxia rating scales in children between 4 – 16 years of age

	DIS	DIS-D	BFMMS	BFMDS	SARA	ICARS	BARS
DIS		0.85	0.29	0.43	0.38	0.15	0.35
DIS-D			0.38	0.44	0.40	0.21	0.37
BFMMS				0.79	0.85	0.69	0.92
BFMDS					0.94	0.52	0.88
SARA						0.61	0.92
ICARS							0.62
BARS							

Regression coefficients of dyskinesia (DIS), dystonia (DIS-D and BFMMS) and ataxia (ICARS, SARA and BARS) rating scales revealed no significant differences; DIS = Dyskinesia Impairment Scale; DIS-D = DIS Dystonia subscale; BFMMS = Burke-Fahn-Marsden Movement Scale; BFMDS = Burke-Fahn-Marsden Disability Scale; SARA = Scale for the Assessment and Rating of Ataxia; ICARS = International Cooperative Ataxia Rating Scale; BARS = Brief Ataxia Rating Scale

Appendix A. Definition of movement disorders and movement disorder-like features

Movement disorder	Description
Dyskinesia	A movement disorder that encompasses a broad spectrum of hyperkinetic movements and can be differentiated into dystonia and choreoathetosis.[23,24]
Dystonia	A movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements and/or postures.[25]
Choreoathetosis	A movement disorders characterized by the combination of chorea (i.e. ongoing, random-appearing sequence of one or more discrete involuntary movements or movement fragments) and athetosis (i.e. slow, continuous, involuntary writhing movements that prevent maintenance of a stable posture).[11,26]
Ataxia	A movement disorders characterized by an impairment of the smooth performance of goal-directed movements, resulting in impaired 'unconscious' decision making about balance, speed, force and direction of intended movements.[27-29]
Movement disorder-like features	Physiological movement features of healthy children that induce falsely positive scores according to official dyskinesia (DIS), dystonia (BFMMS) and ataxia (SARA, ICARS and BARS) rating scale guidelines. These features are not phenotyped as *pathologic*.
Dyskinetic-like features	These physiologic movement features may resemble dyskinesia, such as dystonic- and choreoathetotic-like features (see below).
Dystonic-like features	These physiologic movement features may resemble dystonia, such as suboptimal hand posturing during drawing and walking, grimacing movements of the mouth and overflow movements during finger tapping, see supplementary video.
Choreoathetotic-like features	These physiologic movement features may resemble choreoathetosis, such as saccadic eye movements, fragmented movements of the neck and wriggling movements of hands and feet, see supplementary video.
Ataxic-like features	These physiologic movement features may resemble ataxia, such as suboptimal coordination during walking with feet in tandem position, standing on one leg, fast alternating hand movements and drawing, see supplementary video.

Appendix B: Rating scales characteristics

DYSKINESIA IMPAIRMENT SCALE (DIS)

The Dyskinesia Impairment Scale (DIS) is a recently developed quantitative assessment tool for children with dyskinetic cerebral palsy. The DIS-Total consists of the sum of the dystonia and a choreoathetosis subscales (DIS-D and DIS-C). Both subscales quantify the duration and amplitude of dystonia or choreoathetosis in 12 body regions, involving the eyes, mouth, neck, trunk, proximal and distal limbs on each side. Scores range from zero (optimal) to 288 (maximum) for both subscales.[11]

BURKE-FAHN-MARSDEN DYSTONIA RATING SCALE (BFMDRS)

The Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) is a universally applied biomarker for the severity of dystonia. The BFMDRS consists of the sum of a movement (Burke-Fahn-Marsden Movement Scale [BFMMS]) and a disability subscale (Burke- Fahn-Marsden Disability Scale [BFMDS]).(Burke et al. 1985) The BFMMS quantifies the severity and provoking factor of dystonia in 9 body regions, including the eyes, mouth, speech and swallowing, neck, trunk, arms, and legs. Scores range from zero (optimal) to 120 (maximum). The BFMDS is a functional marker consisting of parental- or self-reported daily activities (involving speech, handwriting, feeding, eating, swallowing, hygiene, dressing, and walking), with scores ranging from 0 (completely independent) to 30 (completely dependent).[30]

ATAXIA RATING SCALES

Universally applied markers for the severity of ataxia are the Scale for Assessment and Rating of Ataxia (SARA), the International Cooperative Ataxia Rating Scale (ICARS) and its derivate, the Brief Ataxia Rating Scale (BARS). The assessed ataxia parameters comprise four different domains: (1) posture and gait; (2) kinetic limb function; (3) speech and (4) oculomotor function (only in ICARS and BARS). Scores range from zero (optimal) to a maximum of 40, 100 and 30 for SARA, ICARS and BARS, respectively.[31-33]